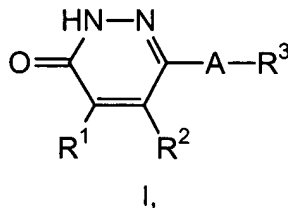


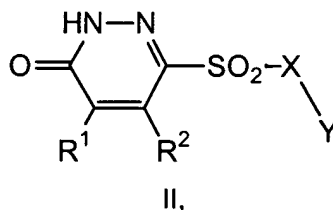
AMENDMENTS TO THE CLAIMS

1(original). A pharmaceutical composition comprising a first compound selected from:

a compound of formula I



and a compound of formula II



or a prodrug of said first compound, or a pharmaceutically acceptable salt of said first compound or said prodrug,

wherein:

A is S, SO or SO₂;

R¹ and R² are each independently hydrogen or methyl;

R³ is Het¹, -CHR⁴Het¹ or NR⁶R⁷;

R⁴ is hydrogen or (C₁-C₃)alkyl;

R⁶ is (C₁-C₆)alkyl, aryl or Het²;

R⁷ is Het³;

Het¹ is pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, phthalazinyl, cinnolyl, naphthyridinyl, pteridinyl, pyrazinopyrazinyl, pyrazinopyridazinyl, pyrimidopyridazinyl, pyrimidopyrimidyl, pyridopyrimidyl, pyridopyrazinyl, pyridopyridazinyl, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, pyrrolopyridyl, furopyridyl, thienopyridyl, imidazolopyridyl, oxazolopyridyl, thiazolopyridyl, pyrazolopyridyl, isoxazolopyridyl, isothiazolopyridyl, pyrrolopyrimidyl, fuopyrimidyl, thienopyrimidyl, imidazolopyrimidyl, oxazolopyrimidyl, thiazolopyrimidyl, pyrazolopyrimidyl, isoxazolopyrimidyl, isothiazolopyrimidyl, pyrrolopyrazinyl, fuopyrazinyl, thienopyrazinyl, imidazolopyrazinyl, oxazolopyrazinyl, thiazolopyrazinyl, pyrazolopyrazinyl, isoxazolopyrazinyl, isothiazolopyrazinyl, pyrrolopyridazinyl, fuopyridazinyl, thienopyridazinyl,

imidazolopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl, pyrazolopyridazinyl, isoxazolopyridazinyl or isothiazolopyridazinyl; Het¹ is independently optionally substituted with up to a total of four substituents independently selected from R⁸, R⁹, R¹⁰ and R¹¹; wherein R⁸, R⁹, R¹⁰ and R¹¹ are each taken separately and are each independently halo, formyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylenyloxycarbonyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C(OH)R¹²R¹³, (C₁-C₄)alkylcarbonylamido, (C₃-C₇)cycloalkylcarbonylamido, phenylcarbonylamido, phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, (C₁-C₄)alkylsulfenyl, (C₁-C₄)alkylsulfonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkyl optionally substituted with up to three fluoro or (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, in the definition of R⁸, R⁹, R¹⁰ and R¹¹ are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkyl optionally substituted with up to five fluoro and (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of R⁸, R⁹, R¹⁰ and R¹¹ are optionally substituted with up to two substituents independently selected from hydroxy, halo, C₁-C₄alkyl, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C₁-C₄alkyl-phenyl optionally substituted in the phenyl portion with one Cl, Br, OMe, Me or SO₂-phenyl wherein said SO₂-phenyl is optionally substituted in the phenyl portion with one Cl, Br, OMe, Me, (C₁-C₄)alkyl optionally substituted with up to five fluoro, or (C₁-C₄)alkoxy optionally substituted with up to three fluoro; R¹² and R¹³ are each independently hydrogen or (C₁-C₄)alkyl;

Het² and Het³ are each independently imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy; Het² and Het³ are each independently optionally substituted with up to a total of four substituents independently selected from R¹⁴, R¹⁵, R¹⁶ and R¹⁷, wherein R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are each taken separately and are each independently halo, formyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylenyloxycarbonyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C(OH)R¹⁸R¹⁹, (C₁-C₄)alkylcarbonylamido, (C₃-C₇)cycloalkylcarbonylamido, phenylcarbonylamido, phenyl,

naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, (C₁-C₄)alkylsulfenyl, (C₁-C₄)alkylsulfonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkyl optionally substituted with up to three fluoro or (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, in the definition of R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkyl optionally substituted with up to five fluoro and (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are optionally substituted with up to two substituents independently selected from hydroxy, halo, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkyl optionally substituted with up to five fluoro and (C₁-C₄)alkoxy optionally substituted with up to three fluoro; and R¹⁸ and R¹⁹ are each independently hydrogen or (C₁-C₄)alkyl;

X and Y together are CH₂-CH(OH)-Ar or CH₂-C(O)-Ar, or

X is a covalent bond, NR²⁰ or CHR²¹, wherein, R²⁰ is (C₁-C₃)alkyl or a phenyl that is optionally substituted with one or more substituents selected from OH, F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, S(O)_n-(C₁-C₆)alkyl and SO₂—NR²²R²³, and R²¹ is hydrogen or methyl, and

Y is a phenyl or naphthyl ring optionally substituted with one or more substituents selected from Ar, OH, F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, S(O)_n-(C₁-C₆)alkyl and SO₂—NR²²R²³;

Ar is a phenyl or naphthyl ring optionally substituted with one or more substituents selected from F, Cl, Br, I, CN, CF₃, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, S(O)_n-(C₁-C₆)alkyl and SO₂—NR²²R²³;

n is independently for each occurrence 0, 1 or 2;

R²² is independently for each occurrence H, (C₁-C₆)alkyl, phenyl or naphthyl;

and

R²³ is independently for each occurrence (C₁-C₆)alkyl, phenyl or naphthyl,

provided that when R³ is NR⁶R⁷, then A is SO₂; and

a second compound that is a cyclooxygenase-2 inhibitor, a prodrug of said second compound or a pharmaceutically acceptable salt of said second compound or said prodrug.

2(original). A composition of claim 1 wherein said first compound is a compound of formula I, wherein A is SO₂; R¹ and R² are each hydrogen; R³ is Het¹, wherein Het¹ is 5H-furo-[3,2c]pyridin-4-one-2-yl, furano[2,3b]pyridin-2-yl, thieno[2,3b]pyridin-2-yl, indol-2-yl, indol-3-yl, benzofuran-2-yl, benzothien-2-yl, imidazo[1,2a]pyridin-3-yl, pyrrol-1-yl, imidazol-1-yl, indazol-1-yl, tetrahydroquinol-1-yl or tetrahydroindol-1-yl, wherein said Het¹ is optionally independently substituted with up to a total of two substituents each independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, hydroxy, benzyl or phenyl; said benzyl and phenyl are each optionally independently substituted with up to three halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, (C₁-C₆)alkylsulfinyl, (C₁-C₆)alkylsulfenyl, trifluoromethyl or hydroxy, or a prodrug thereof or a pharmaceutically acceptable salt of said compound or prodrug.

3(original). A composition of claim 2 wherein Het¹ is indol-2-yl, benzofuran-2-yl, benzothiophen-2-yl, furano[2,3b]pyridin-2-yl, thieno[2,3b]pyridin-2-yl or imidazo[1,2a]pyridin-4-yl, wherein said Het¹ is optionally independently substituted with up to a total of two substituents independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl and phenyl; said phenyl being optionally substituted with up to two substituents independently selected from fluoro, chloro and (C₁-C₆)alkyl.

4(original). A composition of claim 1 wherein said first compound is selected from: 6-(3-trifluoromethyl-benzenesulfonyl)-2H-pyridazin-3-one;

6-(4-bromo-2-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;

6-(4-trifluoromethyl-benzenesulfonyl)-2H-pyridazin-3-one;

6-(2-bromo-benzenesulfonyl)-2H-pyridazin-3-one;

6-(3,4-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;

6-(4-methoxy-benzenesulfonyl)-2H-pyridazin-3-one;

6-(3-bromo-benzenesulfonyl)-2H-pyridazin-3-one;

6-(biphenyl-4-sulfonyl)-2H-pyridazin-3-one;

6-(4'-fluoro-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;

6-(4'-trifluoromethyl-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;

6-(3',5'-bis-trifluoromethyl-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;

6-(biphenyl-2-sulfonyl)-2H-pyridazin-3-one;

6-(4'-trifluoromethyl-biphenyl-2-sulfonyl)-2H-pyridazin-3-one;

6-(2-hydroxy-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2-chloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(3-chloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,3-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,5-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(4-chloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,3-difluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,4-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,4-difluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,6-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2-chloro-4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2-bromo-4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one; and
6-(naphthalene-1-sulfonyl)-2H-pyridazin-3-one,

or a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

5(original). A composition of claim 1 wherein said second compound is selected from celecoxib, rofecoxib and etoricoxib or a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

6(original). A pharmaceutical composition of claim 1 wherein said first compound is in an aldose reductase inhibiting amount.

7(original). A pharmaceutical composition of claim 1 wherein said second compound is present in a cyclooxygenase-2 inhibiting amount.

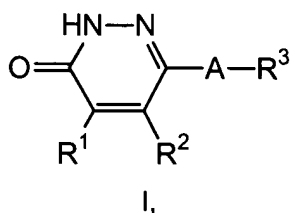
8(original). A pharmaceutical composition of claim 6 wherein said second compound is present in a cyclooxygenase-2 inhibiting amount.

9(original). A pharmaceutical composition of claim 1 further comprising a vehicle, diluent or carrier.

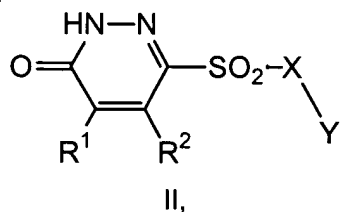
10-19(cancelled).

20(original). A therapeutic method comprising administering to a mammal in need of treatment or prevention of cardiac tissue ischemia a first compound selected from:

a compound of formula I



and a compound of formula II



or a prodrug of said first compound, or a pharmaceutically acceptable salt of said first compound or said prodrug,

wherein:

A is S, SO or SO₂;

R¹ and R² are each independently hydrogen or methyl;

R³ is Het¹, -CHR⁴Het¹ or NR⁶R⁷;

R⁴ is hydrogen or (C₁-C₃)alkyl;

R⁶ is (C₁-C₆)alkyl, aryl or Het²;

R⁷ is Het³;

Het¹ is pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, phthalazinyl, cinnolyl, naphthyridinyl, pteridinyl, pyrazinopyrazinyl, pyrazinopyridazinyl, pyrimidopyridazinyl, pyrimidopyrimidyl, pyridopyrimidyl, pyridopyrazinyl, pyridopyridazinyl, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, pyrrolopyridyl, furopyridyl, thienopyridyl, imidazolopyridyl, oxazolopyridyl, thiazolopyridyl, pyrazolopyridyl, isoxazolopyridyl, isothiazolopyridyl, pyrrolopyrimidyl, furopyrimidyl, thienopyrimidyl, imidazolopyrimidyl, oxazolopyrimidyl, thiazolopyrimidyl, pyrazolopyrimidyl, isoxazolopyrimidyl, isothiazolopyrimidyl, pyrrolopyrazinyl, fuopyrazinyl, thienopyrazinyl, imidazolopyrazinyl, oxazolopyrazinyl, thiazolopyrazinyl, pyrazolopyrazinyl, isoxazolopyrazinyl, isothiazolopyrazinyl, pyrrolopyridazinyl, fuopyridazinyl, thienopyridazinyl, imidazolopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl, pyrazolopyridazinyl, isoxazolopyridazinyl or isothiazolopyridazinyl; Het¹ is independently optionally substituted with up to a total of four substituents independently selected from R⁸, R⁹, R¹⁰ and R¹¹; wherein R⁸, R⁹, R¹⁰ and R¹¹ are each taken separately and are each independently halo, formyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylenyloxycarbonyl, (C₁-

C₄)alkoxy-(C₁-C₄)alkyl, C(OH)R¹²R¹³, (C₁-C₄)alkylcarbonylamido, (C₃-C₇)cycloalkylcarbonylamido, phenylcarbonylamido, phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, (C₁-C₄)alkylsulfenyl, (C₁-C₄)alkylsulfonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkyl optionally substituted with up to three fluoro or (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, in the definition of R⁸, R⁹, R¹⁰ and R¹¹ are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkyl optionally substituted with up to five fluoro and (C₁-C₄)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of R⁸, R⁹, R¹⁰ and R¹¹ are optionally substituted with up to two substituents independently selected from hydroxy, halo, C₁-C₄)alkyl, hydroxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C₁-C₄)alkyl-phenyl optionally substituted in the phenyl portion with one Cl, Br, OMe, Me or SO₂-phenyl wherein said SO₂-phenyl is optionally substituted in the phenyl portion with one Cl, Br, OMe, Me, (C₁-C₄)alkyl optionally substituted with up to five fluoro, or (C₁-C₄)alkoxy optionally substituted with up to three fluoro;

R¹² and R¹³ are each independently hydrogen or (C₁-C₄)alkyl;

Het² and Het³ are each independently imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy; Het² and Het³ are each independently optionally substituted with up to a total of four substituents independently selected from R¹⁴, R¹⁵, R¹⁶ and R¹⁷, wherein R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are each taken separately and are each independently halo, formyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylenyloxycarbonyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, C(OH)R¹⁸R¹⁹, (C₁-C₄)alkylcarbonylamido, (C₃-C₇)cycloalkylcarbonylamido, phenylcarbonylamido, phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, (C₁-C₄)alkylsulfenyl, (C₁-C₄)alkylsulfonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkyl optionally substituted with up to three fluoro or (C₁-C₄)alkoxy optionally substituted with

up to five fluoro; said phenyl, naphthyl, imidazolyl, pyridyl, triazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothiazolyl, pyrrolyl, pyrazolyl, quinolyl, isoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfonyl, furanyl, phenoxy, thiophenoxy, in the definition of R^{14} , R^{15} , R^{16} and R^{17} are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-(C_1 - C_4)alkyl, (C_1 - C_4)alkoxy-(C_1 - C_4)alkyl, (C_1 - C_4)alkyl optionally substituted with up to five fluoro and (C_1 - C_4)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of R^{14} , R^{15} , R^{16} and R^{17} are optionally substituted with up to two substituents independently selected from hydroxy, halo, hydroxy-(C_1 - C_4)alkyl, (C_1 - C_4)alkoxy-(C_1 - C_4)alkyl, (C_1 - C_4)alkyl optionally substituted with up to five fluoro and (C_1 - C_4)alkoxy optionally substituted with up to three fluoro; and R^{18} and R^{19} are each independently hydrogen or (C_1 - C_4)alkyl;

X and Y together are $CH_2-CH(OH)-Ar$ or $CH_2-C(O)-Ar$, or

X is a covalent bond, NR^{20} or CHR^{21} , wherein, R^{20} is (C_1 - C_3)alkyl or a phenyl that is optionally substituted with one or more substituents selected from OH, F, Cl, Br, I, CN, CF_3 , (C_1 - C_6)alkyl, O-(C_1 - C_6)alkyl, $S(O)_n$ -(C_1 - C_6)alkyl and $SO_2-NR^{22}R^{23}$, and R^{21} is hydrogen or methyl, and

Y is a phenyl or naphthyl ring optionally substituted with one or more substituents selected from Ar, OH, F, Cl, Br, I, CN, CF_3 , (C_1 - C_6)alkyl, O-(C_1 - C_6)alkyl, $S(O)_n$ -(C_1 - C_6)alkyl and $SO_2-NR^{22}R^{23}$;

Ar is a phenyl or naphthyl ring optionally substituted with one or more substituents selected from F, Cl, Br, I, CN, CF_3 , (C_1 - C_6)alkyl, O-(C_1 - C_6)alkyl, $S(O)_n$ -(C_1 - C_6)alkyl and $SO_2-NR^{22}R^{23}$;

n is independently for each occurrence 0, 1 or 2;

R^{22} is independently for each occurrence H, (C_1 - C_6)alkyl, phenyl or naphthyl; and

R^{23} is independently for each occurrence (C_1 - C_6)alkyl, phenyl or naphthyl,

provided that when R^3 is NR^6R^7 , then A is SO_2 ,

and a second compound that is a cyclooxygenase-2 inhibitor, a prodrug of said second compound or a pharmaceutically acceptable salt of said second compound or said prodrug.

21(original). A therapeutic method of claim 20 wherein said first compound is a compound of formula I, wherein A is SO_2 ; R^1 and R^2 are each hydrogen; R^3 is Het^1 , wherein Het^1 is 5H-furo-[3,2c]pyridin-4-one-2-yl, furano[2,3b]pyridin-2-yl, thieno[2,3b]pyridin-2-yl, indol-2-yl, indol-3-yl, benzofuran-2-yl, benzothien-2-yl,

imidazo[1,2a]pyridin-3-yl, pyrrol-1-yl, imidazol-1-yl, indazol-1-yl, tetrahydroquinol-1-yl or tetrahydroindol-1-yl, wherein said Het¹ is optionally independently substituted with up to a total of two substituents each independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, hydroxy, benzyl or phenyl; said benzyl and phenyl are each optionally independently substituted with up to three halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, (C₁-C₆)alkylsulfinyl, (C₁-C₆)alkylsulfenyl, trifluoromethyl or hydroxy, or a prodrug thereof or a pharmaceutically acceptable salt of said compound or prodrug.

22(original). A therapeutic method of claim 21 wherein Het¹ is indol-2-yl, benzofuran-2-yl, benzothiophen-2-yl, furano[2,3b]pyridin-2-yl, thieno[2,3b]pyridin-2-yl or imidazo[1,2a]pyridin-4-yl, wherein said Het¹ is optionally independently substituted with up to a total of two substituents independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl and phenyl; said phenyl being optionally substituted with up to two substituents independently selected from fluoro, chloro and (C₁-C₆)alkyl.

23(original). A therapeutic method of claim 20 wherein said first compound is selected from: 6-(3-trifluoromethyl-benzenesulfonyl)-2H-pyridazin-3-one;

6-(4-bromo-2-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;

6-(4-trifluoromethyl-benzenesulfonyl)-2H-pyridazin-3-one;

6-(2-bromo-benzenesulfonyl)-2H-pyridazin-3-one;

6-(3,4-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;

6-(4-methoxy-benzenesulfonyl)-2H-pyridazin-3-one;

6-(3-bromo-benzenesulfonyl)-2H-pyridazin-3-one;

6-(biphenyl-4-sulfonyl)-2H-pyridazin-3-one;

6-(4'-fluoro-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;

6-(4'-trifluoromethyl-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;

6-(3',5'-bis-trifluoromethyl-biphenyl-4-sulfonyl)-2H-pyridazin-3-one;

6-(biphenyl-2-sulfonyl)-2H-pyridazin-3-one;

6-(4'-trifluoromethyl-biphenyl-2-sulfonyl)-2H-pyridazin-3-one;

6-(2-hydroxy-benzenesulfonyl)-2H-pyridazin-3-one;

6-(2-chloro-benzenesulfonyl)-2H-pyridazin-3-one;

6-(3-chloro-benzenesulfonyl)-2H-pyridazin-3-one;

6-(2,3-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;

6-(2,5-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;

6-(4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;

6-(4-chloro-benzenesulfonyl)-2H-pyridazin-3-one;

6-(2-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,3-difluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,4-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,4-difluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2,6-dichloro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2-chloro-4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one;
6-(2-bromo-4-fluoro-benzenesulfonyl)-2H-pyridazin-3-one; and
6-(naphthalene-1-sulfonyl)-2H-pyridazin-3-one,

or a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

24(original). A therapeutic method of claim 20 wherein said second compound is selected from celecoxib, rofecoxib and etoricoxib or a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

25(original). A therapeutic method of claim 20 wherein said first compound is administered in an aldose reductase inhibiting amount.

26(original). A therapeutic method of claim 20 wherein said second compound is administered in a cyclooxygenase-2 inhibiting amount.

27(original). A therapeutic method of claim 25 wherein said second compound is administered in a cyclooxygenase-2 inhibiting amount.

28(original). A therapeutic method of claim 20 wherein said mammal is a human.